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2.	Patent application number *(The Patent Office will fill in this part)*	9914623.5
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG SCHWARZWALDALLEE 215 4058 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Organic compounds
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH
	Patents ADP number *(if you know it)*	1800001

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Signature	Date
B.A. Yorke & Co.	**23.06.99**

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10/018929
531 Rec'd PCT/PTO 21 DEC 2001

Organic Compounds

The present invention relates to DNA which encodes proteins that control gene silencing, and particularly the silencing of plant genes.

The loss of expression of previously active genes in plants, also referred to as gene silencing, is observed in response to developmental, environmental or unknown signals. It occurs at a frequency higher than that of mutations, yet it is markedly stable during somatic transmission. Gene silencing, initially perceived as an unwanted source of instability of transgene expression, is now regarded as a molecular tool to intentionally regulate gene expression.

It appears that chromosomal position or structure of the affected loci are factors determining the frequency and strength of silencing. Inactivation seems to preferentially affect genes present in multiple copies and is thought to be a consequence of sequence redundancy. Many examples of homology-dependent gene silencing have been reported. Closer analysis has allowed the classification of silencing events according to the relative position of the affected loci (*cis*, *trans*, allelic, ectopic), the origin of the affected genes (endogenous or transgenic), and the level of interaction (transcriptional or post-transcriptional). While post-transcriptional silencing seems to mainly involve the formation of aberrant RNA molecules and is occasionally, but not necessarily, accompanied by DNA methylation, silencing interfering with transcription initiation is more strictly correlated with hypermethylation of the DNA and possibly with alteration of chromatin structure at the silent loci. It is, however, not clear whether these molecular events are a prerequisite for gene silencing or a consequence of the silent state.

In the case of transcriptional silencing, the inactive state of silenced genes is stably transmitted through mitotic and meiotic divisions. As in other organisms, trans-acting modifier loci are assumed to be responsible for the stability of the inactive state of the silenced genes. Mutations in such loci resulting in mutated proteins are expected to result in reduced gene silencing and reactivation of previously silent loci by interfering with the maintenance of the silent state, or by a failure to recognize sequence redundancy. It has been reported that mutations in the DDM1 gene of Arabidopsis thaliana release

transcriptional gene silencing and that this genes encodes a SWI2/SNF2-like protein involved in chromatin remodeling. However, mutation of the DDM1 gene causes severe pleiotropic effects. Therefore, to be able to modify such effects making use of gene technology, it is necessary to identify further specific modifier loci and charactize the corresponding wild-type and mutant proteins. It is the main objective of the present invention to provide DNA comprising an open reading frame encoding such a protein.

Trans-acting modifier loci according to the present invention can be identified by T-DNA insertion mutagenesis as described in Example 1 for an Arabidopsis line carrying a heritably inactivated, methylated hygromycin resistance gene. A mutation of a silencing modifier locus results in release of silencing of the hygromycin resistance gene and restores hygromycin resistance. Plants homozygous for the silent resistance gene are subjected to transformation with a selectable marker gene different from the hygromycin resistance gene, which is under the control of the T-DNA 1'-2' dual promoter. Transformants are selected and their progeny screened for hygromycin resistance. The mutant phenotype (hygromycin resistance) is screened for genetic co-segregation with a specific T-DNA insert. Cloning of the tagged gene using routine methods of recombinant DNA technology allows to characterize the mutant and wild-type DNA sequence of the silencing modifier locus as well as the encoded protein.

Within the context of the present invention reference to a gene is to be understood as reference to a DNA coding sequence associated with regulatory sequences, which allow transcription of the coding sequence into RNA such as mRNA, rRNA, tRNA, snRNA, sense RNA or antisense RNA. Examples of regulatory sequences are promoter sequences, 5' and 3' untranslated sequences, introns, and termination sequences.

A promoter is understood to be a DNA sequence initiating transcription of an associated DNA sequence, and may also include elements that act as regulators of gene expression such as activators, enhancers, or repressors.

Expression of a gene refers to its transcription into RNA or its transcription and subsequent translation into protein within a living cell. In the case of antisense constructs expression refers to the transcription of the antisense DNA only.

The term transformation of cells designates the introduction of nucleic acid into a host cell, particularly the stable integration of a DNA molecule into the genome of said cell.

Any part or piece of a specific nucleotide or amino acid sequence is referred to as a component sequence.

DNA according to the present invention comprises an open reading frame encoding a protein characterized by an amino acid sequence comprising a component sequence of at least 150 amino acid residues having 40% or more identity with SEQ ID NO: 3. In particular the protein encoded by the open reading frame can be described by the formula R_1-R_2-R_3, wherein

-- R_1, R_2 and R_3 constitute component sequences consisting of amino acid residues independently selected from the group of the amino acid residues Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, and His,

-- R_1 and R_3 consist independently of 0 to 3000 amino acid residues;

-- R_2 consists of at least 150 amino acid residues; and

-- R_2 is at least 40% identical to an aligned component sequence of SEQ ID NO: 3.

In most cases the total length of the protein will be in the range of 1000 to 3000 amino acid residues. In preferred embodiments of the invention the component sequence R_2 consists of at least 200 amino acid residues. Specific examples of the component sequence R_2 are component sequences of SEQ ID NO: 3 represented by the following range of amino acids:

1 - 416 (corresponding to exon 2);
418 - 583 (corresponding to exons 3 to 5);
584 - 890 (corresponding to exon 6);
892 - 1472 (corresponding to exons 7 to 9);
1007 - 1472 (corresponding to exon 9);
1473 - 1631 (corresponding to exons 10 to 12);
1632 - 1827 (corresponding to exons 13 to 15); and
1829 - 2001 (corresponding to exon 16).

In a preferrred embodiment of the present invention at least one of the component sequences R_1 or R_3 comprises one or more additional component sequences with a length of at least 50 amino acids and at least 60% identical to an aligned component sequence of SEQ ID NO: 3. Specific examples of such additional component sequences are component sequences of SEQ ID NO: 3 represented by the following range of amino acids:

420 - 525 (corresponding to exons 3 and 4);
444 - 525 (corresponding to exon 4);
526 - 583 (corresponding to exon 5);
892 - 971 (corresponding to exon 7);
892 - 1006 (corresponding to exons 7 and 8);
1473 - 1524 (corresponding to exon 10);
1525 - 1576 (corresponding to exon 11);
1577 - 1631 (corresponding to exon 12);
1632 - 1690 (corresponding to exons 13);
1692 - 1757 (corresponding to exons 14); and
1758 - 1827 (corresponding to exons 15).

Dynamic programming algorithms yield different kinds of alignments. In general there exist two approaches towards sequence alignment. Algorithms as proposed by Needleman & Wunsch and by Sellers align the entire length of two sequences providing a global alingment of the sequences. The Smith-Waterman algorithm on the other hand yields local alignments. A local alignment aligns the pair of regions within the sequences that are most similiar given the choice of scoring matrix and gap penalties. This allows a database search to focus on the most highly conserved regions of the sequences. It also allows similiar domains within sequences to be identified. To speed up alignments using the Smith-Waterman algorithm both BLAST (Basic Local Alignment Search Tool) and FASTA place additional restrictions on the alignments.

Within the context of the present invention alignments are conveniently performed using BLAST, a set of similarity search programs designed to explore all of the available sequence databases regardless of whether the query is protein or DNA. Version BLAST 2.0 (Gapped BLAST) of this search tool has been made publicly available on the internet (currently http://www.ncbi.nlm.nih.gov/BLAST/). It uses a heuristic algorithm which seeks local as opposed to global alignments and is therefore able to detect relationships among sequences which share only isolated regions. The scores assigned in a BLAST search have a well-defined statistical interpretation. Particularly useful within the scope of the present invention are the blastp program allowing for the introduction of gaps in the local sequence alignments and the PSI-BLAST program, both programs comparing an amino acid query sequence against a protein sequence database, as well as a blastp variant program

allowing local alignment of two sequences only. Said programs are preferably run with optional parameters set to the default values.

Sequence alignments using BLAST can also take into account whether the substitution of one amino acid for another is likely to conserve the physical and chemical properties necessary to maintain the structure and function of the protein or is more likely to disrupt essential structural and functional features of a protein. Such sequence similarity is quantified in terms of a percentage of "positive" amino acids, as compared to the percentage of identical amino acids and can help assigning a protein to the correct protein family in border-line cases.

Sequence alignments using such computer programs reveal the presence of an ATP/GTP-binding motif A (amino acids 460 to 467 in SEQ ID NO:3), the consensus sequence of which is (Ala/Gly)XaaXaaXaaXaaGlyLys(Ser/Thr), wherein (Ala/Gly) indicates Ala or Gly, Xaa indicates any naturally occuring amino acid and (Ser/Thr) indicates Ser or Thr. Alignment additionally reveals a region (amino acid position 479 to 719 in SEQ ID: 3), similiar to part of the ATPase/helicase domain of proteins in the SWI2/SNF2 family which are involved in chromatin remodeling but no significant overall sequence identity with known proteins.

Specific examples of DNA according to the present invention are described in SEQ ID NO: 1 and SEQ iD NO: 2 encoding an Arabidopsis protein described in SEQ ID NO: 3. Stretches of SEQ ID NO: 3 having 50 to 500 amino acids length can show between 20 and 50% sequence identity to stretches of known protein sequences after alignment. Overall alignments of SEQ ID NO: 3, however, result in sequence identities lower than 30%. Thus, the present invention defines a new protein family the members of which are characterized by an amino acid sequence comprising a component sequence of at least 150 amino acid residues having 40% or more identity with an aligned component sequence of SEQ ID NO: 3. Preferably the amino acid sequence identity is higher than 50% or even higher than 55%.

DNA encoding proteins belonging to the new protein family according to the present invention can be isolated from monocotyledonous and dicotyledonous plants. Preferred sources are corn, sugarbeet, sunflower, winter oilseed rape, soybean, cotton, wheat, rice,

potato, broccoli, cauliflower, cabbage, cucumber, sweet corn, daikon, garden beans, lettuce, melon, pepper, squash, tomato, or watermelon. However, they can also be isolated from mammalian sources such as mouse or human tissues. The following general method, can be used, which the person skilled in the art knows to adapt to the specific task. A single stranded fragment of SEQ ID NO: 1 or SEQ ID NO: 2 consisting of at least 15, prefeably 20 to 30 or even more than 100 consecutive nucleotides is used as a probe to screen a DNA library for clones hybridizing to said fragment. The factors to be observed for hybridization are described in Sambrook et al, Molecular cloning: A laboratory manual, Cold Spring Harbor Laboratory Press, chapters 9.47-9.57 and 11.45-11.49, 1989. Hybridizing clones are sequenced and DNA of clones comprising a complete coding region encoding a protein characterized by an amino acid sequence comprising a component sequence of at least 150 amino acid residues having 40% or more sequence identity to SEQ ID NO: 3 is purified. Said DNA can then be further processed by a number of routine recombinant DNA techniques such as restriction enzyme digestion, ligation, or polymerase chain reaction analysis.

The disclosure of SEQ ID NO: 1 and SEQ ID NO: 2 enables a person skilled in the art to design oligonucelotides for polymerase chain reactions which attempt to amplify DNA fragments from templates comprising a sequence of nucleotides characterized by any continuous sequence of 15 and preferably 20 to 30 or more basepairs in SEQ ID NO: 1 or SEQ ID NO: 2. Said nucleotides comprise a sequence of nucleotides which represents 15 and preferably 20 to 30 or more basepairs of SEQ ID NO: 1 or SEQ ID NO: 2. Polymerase chain reactions performed using at least one such oligonucleotide and their amplification products constitute another embodiment of the present invention.

EXAMPLES:

Example 1: ***T-DNA Insertion***

Transgenic line A of *Arabidopsis thaliana* ecotype Zürich with a transcriptionally silenced locus containing multiple copies of a chimeric hygromycin phosphotransferase gene (*hpt*) has been described in Mittelsten Scheid et al, Mol Gen Genet 228: 104-112, 1991 and Mittelsten Scheid et al, Proc Natl Acad Sci USA 93: 7114-7119, 1996. A homozygous,

diploid genotype of said line is subjected to *Agrobacterium* mediated gene transfer by *in planta* vacuum infiltration (Bechtold et al., C R Acad Sci Paris Life Science 316: 1194-1199, 1993) generating more than 4000 independent T-DNA transformants. The binary vector with T-DNA consisting of the coding region of the *bar* gene transcriptionally fused to the 1' promoter (p1'barbi), the *Agrobacterium* strain (C58CIRif^R) and the transformation protocol are described by Mengiste et al, Plant J 12: 945-948, 1997. Transformants (T1 plants) are selected by repeated spraying of germinated seedlings with Basta solution (150 mg/l) and grown to maturity.

Example 2: ***Mutant Selection***

Selfed seeds (T2 families) are collected from individual transformants. Prior to screening for revertants of the silenced phenotype, seeds are dried for one week at room temperature and cold-treated at 4°C for a minimum of one week. Pooled aliquots of approximately 1000 seeds (consisting of 50 seeds from 20 T2 families) are surface-sterilized twice (with 5% sodium hypochlorite containing 0.1% Tween 80) for 7 min and washed with sterile double-distilled water. For selection, each aliquot is plated on 14-cm Petri dishes containing 75 ml germination medium (according to Masson et al, Plant J 2: 829-933, 1992) solidified with 0.8% agar and containing 10 mg/l hygromycin B (Calbiochem). To ensure equal distribution during sowing, seeds are mixed with 30 ml of the same medium containing 0.4% agar. As positive control two seeds from a hygromycin-resistant line are sown at marked locations on each plate. Plates are cold-treated at 4°C for 2 days and subsequently subjected to alternating periods of 16 hours light at 21°C and 8 hours darkness at 16°C. Hygromycin resistance is evaluated each day for 8-15 days after sowing.

Example 3: ***Molecular and Genetic Analysis of the Mutant***

Following identification of 11 hygromycin-resistant seedlings in one of the pools, the families forming this pool are re-screened individually. One family contains approximately 25% hygromycin-resistant seedlings. Six resistant plantlets of this family are transferred to larger vessels containing germination medium without hygromycin. After rosette formation and development of the root system, plants are transferred to soil for further growth and seed setting. Prior to potting, tissue explants are taken from each plant to generate callus cultures on RCA medium (Table 1) with or without 10 mg/l hygromycin B. Callus cultures are

used as a source of material for DNA and RNA analyses and for a further confirmation of hygromycin resistance in this tissue.

Genomic DNA is isolated using a CTAB based method as described by Mittelsten Scheid et al, Mol Gen Genet 244: 325-330, 1994, and incubated with restriction enzymes *BamHI*, *HpaII*, *MspII*, *DraI*, *EcoRV*, *RcaI* or *HindIII*. Total RNA is obtained using a RNAeasy kit (Qiagen) according to the supplier's recommendation. Southern and northern blot analysis are performed under conditions described by Church and Gilbert, Proc Natl Acad Sci USA 81: 1991-1995, 1984, using DNA fragments labelled with ^{32}P by random prime labeling. The coding region of the *hpt* gene, or DNA consisting of the P35S promoter, *hpt* coding and terminator region, or the coding region of the *bar* gene together with the 1' promoter are used as probes.

Northern blot analysis of 4 hygromycin-resistant siblings shows restoration of transcription of the *hpt* gene. Southern blot analysis of said siblings indicates that there is no detectable rearrangement within the complex *hpt* insert. The *hpt* transgene complex in the mutant is still hypermethylated like in the original line A, as judged by Southern blot analysis with the methylation-sensitive restriction enzymes *HpaII* and *MspI*, and by genomic sequencing of the promoter region aftertreatment with bisulfate. There is also no influence of the mutation on the methylation of repetitive genomic DNA in contrast to that observed for the *som* mutations.

The hygromycin-resistant plants, as well as non-selected siblings from the same family are grown to set seeds, checked for Basta resistance in the next generation, and scored for the number and size of the T-DNA inserts by Southern analysis. The results demonstrate that the original T-DNA transformant must have contained 2 T-DNA insertions segregating independently in the siblings. One insert co-segregates with the hygromycin resistant mutant phenotype. A plant homozygous for this insert and lacking the other T-DNA insert, is used for cloning the corresponding T-DNA insertion site.

Table 1: Composition of RCA medium

RCA medium	
MS macro 10 x	100 ml
B5 micro 1000 x	1 ml

ferric citrate	5 ml
NT vitamins 100 x	10 ml
sucrose	10 g
MES	5 ml
agar	10 g
NAA	0.1 mg
BAP	1 mg
pH 5.8 (KOH)	
ad 1 l	

MS macro 10 x

potassium nitrate	19 g
ammonium nitrate	16.5 g
calcium chloride (x 2 H_2O)	4.4 g
magnesium sulfate (x 7 H_2O)	3.7 g
potassium dihydrogen phosphate	1.7 g
ad 1 l	

B5 micro 1000 x

magnesium sulfate (x H_2O)	1000 mg
boric acid	300 mg
zinc sulfate (x 7 H_2O)	200 mg
potassium iodide	75 mg
sodium molybdate (x 2 H_2O)	25 mg
copper sulfate (x 5 H_2O)	2.5 mg
cobalt chloride (x 6 H_2O)	2.5 mg
ad 100 ml	

ferric citrate

ammonium iron citrate	10 g
ad 1 l	

NT vitamins 100 x

myo-inositol	1000 mg
thiamine HCl	10 mg
ad 1 l	

MES

MES	14 g
pH 6 (NaOH)	
ad 100 ml	

Example 4: ***Cloning of the "Silencing Gene"***

Genomic DNA from the plant containing only the T-DNA co-segregating with the hygromycin resistant mutant phenotype is isolated. The DNA is subjected to TAIL (thermal asymmetric interlaced) PCR according to Liu et al, Plant J 8: 457-463, 1995, using 3 specific, nested primers close to the right border of the T-DNA (5'-CAT CTA CGG CAA TGT ACC AGC-3' (SEQ ID NO: 4), 5'-GAT GGG AAT TGG CTG AGT GGC-3' (SEQ ID NO: 5), 5'-CAG TTC CAA ACG TAA AAC GGC-3' (SEQ ID NO: 6)) which are directed outwards, and one of several degenerate primers which might bind in flanking plant DNA. Two out of the following seven degenerate primers

AD1	5'-NTC GAS TWT SGW GTT-3'	(Liu et al supra; SEQ ID NO: 7)
AD2	5'-NGT CGA SWG ANA WGA A-3'	(Liu et al supra; SEQ ID NO: 8)
AD3	5'-WGT GNA GWA NCA NAG A-3'	(Liu et al supra; SEQ ID NO: 9)
AD4	5'-WGG WAN CWG AWA NGC A-3'	(SEQ ID NO: 10)
AD5	5'-WCG WWG AWC ANG NCG A-3'	(SEQ ID NO: 11)
AD6	5'-WGC NAG TNA GWA NAA G-3'	(SEQ ID NO: 12)
AD7	5'-AWG CAN GNC WGA NAT A-3'	(SEQ ID NO: 13)

actually result in amplification of specific fragments. The larger one obtained using AD7 is cloned and sequenced. It contains 50 bp of the T-DNA and 275 bp of flanking plant DNA. In Southern blot analysis it is shown that this PCR fragment contains the plant DNA flanking the T-DNA. The PCR fragment is used to screen a genomic library (Stratagene) of wild type *Arabidopsis thaliana* ecotype Columbia. Three genomic clones hybridizing to the PCR fragment are identified. The genomic clones are further mapped with restriction enzymes, hybridized to the PCR fragment and aligned to each other. In one of the genomic clones obtained (p4A-11), the sequence found to flank the T-DNA of the insertion mutation is located approximately in the middle of the genomic sequence. An approximately 800 bp EcoRI-Sal I fragment of p4A-11 is used to obtain the overlapping genomic clone p5-6, and an approximately 700 bp EcoRI fragment of p5-6 is used to obtain genomic clone p30-1 overlapping with p5-6. An approximately 700 bp HindIII fragment of p30-1 is used to obtain the genomic clone p33-19 overlapping with p30-1. Said clones are sequenced to design primers for RT-PCR. The approximately 700 bp EcoRI fragment of p5-6 is further used for screening of a cDNA library according to Elledge et al, Proc Natl Acad Sci USA 88: 1731-

1735, 1991). Nine cDNA clones are obtained and the longest clone p17-8 having a length of 2.6 kb is sequenced.

Example 5: ***Sequence Analysis and Alignments***

Taking into account the large size of the Arabidopsis silencing gene cloned above it cannot be entirely excluded that the authentic nucleotide and amino acid sequences of the gene and protein, respectively, might deviate from the sequences given in SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3 at a few positions due to mutations arising from the cloning procedure or due to ambiguities in the sequencing reactions.

The 2.6 kb cDNA clone is analyzed sequentially from both ends and is shown to contain one large ORF as well as a 3' untranslated sequence.

Analysis of the genomic clones reveals that clones p4A-11 and p5-6 contain sequences homologous to the cDNA sequence as well as 7 intron sequences. Comparing the genomic sequences with the DNA sequences flanking the T-DNA insert, it turns out that the T-DNA insertion causes a deletion of about 2 kb of genomic DNA. The 5' end of the deletion is located in an intron (intron 12) and the 3' end of the deletion is located downstream of the 3' end of the cDNA. The sequence of 5' end of the cDNA clone terminates in the middle of the sequence of the genomic clone p5-6. Three independent nested RT-PCR reactions are performed to obtain additional cDNA sequences further upstream. The sequences of the primers used for these RT-PCRs are as follows:

RT1-1	5'-CTGTACATACTGAGTACAATCGGA-3'	(SEQ ID NO: 14)
RT1-2	5'-GCTTCAATTCCTGCCTCAGTTGAAC-3'	(SEQ ID NO: 15)
RT1-3	5'-CTCTACGTGCTTAACATCATGCGA-3'	(SEQ ID NO: 16)
RT1-4	5'-CCAGCTTCTGCTACTAGAAAGTCAG-3'	(SEQ ID NO: 17)
RT2/3-1	5'-CTGGAGTTGCATGAAATCCTGGATG-3'	(SEQ ID NO: 18)
RT2/3-2	5'-GCTCTTTGTAAGCTGTTCACGAGAC-3'	(SEQ ID NO: 19)
RT2-3	5'-TCGCATGATGTTAAGCACGTAGAG-3'	(SEQ ID NO: 20)
RT2-4	5'-GAGTACTGGTCCGTGAACAGGTAAT-3'	(SEQ ID NO: 21)
RT3-3	5'-ATGCTTGCACAAGCATGGTCGGAAA-3'	(SEQ ID NO: 22)
RT3-4	5'-TGCAACATCGTGCATTTGCTCCAGA-3'	(SEQ ID NO: 23)
RT4-1	5'-CACAAGCATGAGTTTTTCCTTCCGG-3'	(SEQ ID NO: 24)
RT4-2	5'-CTGACTTTCTAGTAGCAGAAGCTGG-3'	(SEQ ID NO: 25)

Sequences of several parts of the genomic clones are found to be deposited in the *Arabidopsis* database (accession numbers B67281, B62563, B20434, B20425, B21274, B08967, B11993, B20116, B12496 and B10852 as end sequences of BAC, and Z18494 and AA597930 as partial cDNA sequences, on 13 Apr 1999). A comparison of the encoded protein sequence with the Swiss Protein Database reveals partial similarity with ATPase/helicase proteins of the SWI2/SNF2 family (amino acid position 479 to 719 in SEQ ID NO: 3). The encoded protein consists of 2001 amino acids and is calculated to have a molecular weight of 219 kD and a pI of 5.1. An ATP/GTP-binding motif (amino acid position 460 to 467 in SEQ ID NO: 3) and three nuclear localization motifs (amino acid positions 362 to 367, 832 to 838 and 858 to 862 in SEQ ID NO: 3) are found in the encoded protein. Similarity to the actin binding domain of chicken tensin (amino acid position 1899 to 1941 in SEQ ID NO: 3) and a predicted membrane spanning domain (amino acid position 995 to 1015 in SEQ ID NO: 3) are also detected.

Example 6: ***Homologous genes in other species***

The cDNA clone is used to probe genomic DNA from turnip, tomato, tobacco, maize, mouse, fruit fly and man for the presence of homologous genes by Southern blot analysis. Hybridization under conditions of low stringency is found in all cases. Cross-hybridizing clones from libraries can be identified and sequenced.

Example 7: ***Manipulating marker gene expression by antisense constructs***

The 2.6 kb cDNA fragment and a 1.8 kb RT-PCR fragment amplified by a nested RT-PCR using primers RT1-1 and RT1-2 for the first PCR and primers RT1-3 and RT1-4 for the second PCR, are each inversely cloned into the multiple cloning site of the binary vector pbarbi53 to generate antisense RNA. pbarbi53 is a modified vector of p1'barbi and carries an expression cassette consisting of the 35S promoter of cauliflower mosaic virus, a multiple cloning site containing Xho I, SnaBI, Hpa I and Cla I restriction sites and the 35S terminator of cauliflower mosaic virus at the HindIII site of p1'barbi. The resulting recombinant plasmids are introduced into Agrobacterium as described in Example 1. The transgenic plant line GUS-TS (obtainable from Dr. H. Vaucheret, INRA, Versailles Cedex, France) of Arabidopsis thaliana ecotype Colombia containing a transcriptionally silenced locus with multiple copies of a chimeric beta-glucuronidase (gus) gene, is transformed with the recombinant plasmids as described in Example 1 and transformants are selected as described by Mengiste et al, Plant J 12: 945-948, 1997. pbarbi53 vector DNA is used

in control transformations. The transformants are examined for reactivation of the gus gene by histochemical staining. A cotyledon leaf is soaked in gus staining solution (100 mM sodium phosphate buffer (pH 7.0), 0.05% 5-bromo-4-chloro-3-indolyl-beta-D-glucuronidase, 0.1% sodium azide) under vacuum for 10 min and then incubated at 37°C overnight. While strong gus activity is observed in the plants transformed with the recombinant plasmid carrying the 2.6 kb cDNA, plants transformed with the recombinant plasmid carrying the 1.8 kb RT-PCR fragment or pbarbi53 do not show any gus activity above background. Therefore, expression of the antisense RNA of the 2.6 kb cDNA mimicks the mutant phenotype and confirms that sequences shown in SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3 represent the genetic information for a component of the transcriptional gene silencing system.

What is claimed is:

1. DNA comprising an open reading frame encoding a protein characterized by an amino acid sequence comprising a component sequence of at least 150 amino acid residues having 40% or more identity with an alinged component sequence of SEQ ID NO: 3.

2. The DNA according to claim 1 comprising an open reading frame encoding a protein having the formula R_1-R_2-R_3, wherein
   -- R_1, R_2 and R_3 constitute component sequences consisting of amino acid residues independently selected from the group of the amino acid residues Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, and His,
   -- R_1 and R_3 consist independently of 0 to 3000 amino acid residues;
   -- R_2 consists of at least 150 amino acid residues; and
   -- R_2 is at least 40% identical to an aligned component sequence of SEQ ID NO: 3.

3. The DNA according to claim 1 comprising an open reading frame encoding one or more SWI2/SNF2-like ATPase/helicase motifs.

4. The DNA according to claim 1, wherein the open reading frame encodes a protein characterized by the amino acid sequence of SEQ ID NO: 3

5. The DNA according to claim 1 characterized by the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 2.

6. The DNA according to claim 1, wherein expression of RNA, complementary to mRNA transcribed therefrom, releases silencing of a transgenic marker gene.

7. The protein encoded by the open reading frame of any one of claims 1 to 6.

8. A method of producing DNA according to claim 1, comprising
   - screening a DNA library for clones which are capable of hybridizing to a fragment of the DNA defined by SEQ ID NO: 1 or SEQ ID NO: 2, wherein said fragment has a length of at least 15 nucleotides;
   - sequencing hybridizing clones;
   - purifying vector DNA of clones comprising an open reading frame encoding a protein characterized by an amino acid sequence comprising a component sequence of at least 150 amino acid residues having 40% or more sequence identity to SEQ ID NO: 3
   - optionally further processing the purified DNA.

9. A polymerase chain reaction wherein at least one oligonucleotide used comprises a sequence of nucleotides which represents 15 or more basepairs of SEQ ID NO: 1 or SEQ ID NO: 2.

Organic Compounds

Abstract

The present invention relates to DNA which encodes proteins involved in gene silencing. Related genes encoding proteins characterized by an amino acid sequence comprising a component sequence of at least 150 amino acid residues having 40% or more identity with an alinged component sequence of SEQ ID NO: 3 can be isolated from different sources such as mammalian or plant cells. Further disclosed is a method for isolating DNA according to the invention.

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Asp Val Gln Gly Lys Thr Asp Cys Pro Pro Pro Ala Asp Ala Gly Ser
175                 180                 185                 190

aaa agg ctg cca gtt gac gaa act agt ttg gac aag ggc act gat ttt   927
Lys Arg Leu Pro Val Asp Glu Thr Ser Leu Asp Lys Gly Thr Asp Phe
                195                 200                 205
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cct ttg aaa tca gtt acg gag acc gag aag ata gtg ctt gat gca tcc   975
Pro Leu Lys Ser Val Thr Glu Thr Glu Lys Ile Val Leu Asp Ala Ser
            210                 215                 220

ccc ata gtt gaa act ggg gat gac agt gtt ata ggt tca cca tct gag   1023
Pro Ile Val Glu Thr Gly Asp Asp Ser Val Ile Gly Ser Pro Ser Glu
        225                 230                 235

aat tta gag aca caa aag ctt caa gat ggt aag aca gat tgt tca cca   1071
Asn Leu Glu Thr Gln Lys Leu Gln Asp Gly Lys Thr Asp Cys Ser Pro
    240                 245                 250

cct gca aat gca gaa tcg aaa acg ctg cca gtt ggt gaa act agt tta   1119
Pro Ala Asn Ala Glu Ser Lys Thr Leu Pro Val Gly Glu Thr Ser Leu
255                 260                 265                 270

gaa aaa gaa tat cca caa aag ttt caa gat gat aac aca gat tgt cta   1167
Glu Lys Glu Tyr Pro Gln Lys Phe Gln Asp Asp Asn Thr Asp Cys Leu
                275                 280                 285

cca cct gca aat gca gaa tca aaa agg ctg cca gtt ggc gaa act agt   1215
Pro Pro Ala Asn Ala Glu Ser Lys Arg Leu Pro Val Gly Glu Thr Ser
            290                 295                 300

tta gaa aag gac act gat ttt cct ttg aaa tca act acg gag act gga   1263
Leu Glu Lys Asp Thr Asp Phe Pro Leu Lys Ser Thr Thr Glu Thr Gly
        305                 310                 315

aag atg gtt ctt tat gca tcc ccc ata gtt gaa act agg gat gac agc   1311
Lys Met Val Leu Tyr Ala Ser Pro Ile Val Glu Thr Arg Asp Asp Ser
    320                 325                 330

gtt ata tgt tca cca tct aca aat tta gaa acc caa aag ctt ctt gtc   1359
Val Ile Cys Ser Pro Ser Thr Asn Leu Glu Thr Gln Lys Leu Leu Val
335                 340                 345                 350

agt aaa act ggc tta gaa acc gac ata gtt ttg cct ttg aaa aga aaa   1407
Ser Lys Thr Gly Leu Glu Thr Asp Ile Val Leu Pro Leu Lys Arg Lys
                355                 360                 365

aga gac act gca gaa att gag ctg gat gca tgt gct aca gtt gca aat   1455
Arg Asp Thr Ala Glu Ile Glu Leu Asp Ala Cys Ala Thr Val Ala Asn
            370                 375                 380

gga gat gat cac gtt atg agt tct gat ggg gtc att cca tct cca tct   1503
Gly Asp Asp His Val Met Ser Ser Asp Gly Val Ile Pro Ser Pro Ser
        385                 390                 395

ggg tgc aaa aat gat aat cga cct gaa atg tgc aac acg tgt aaa aaa   1551
Gly Cys Lys Asn Asp Asn Arg Pro Glu Met Cys Asn Thr Cys Lys Lys
    400                 405                 410

cgg caa aag gtc aac ggt gat tgt caa aat agg agt gtt tgc tcc tgc   1599
Arg Gln Lys Val Asn Gly Asp Cys Gln Asn Arg Ser Val Cys Ser Cys
415                 420                 425                 430
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att gtc cag cca gtt gaa gaa tct gat aac gtg aca cag gat atg aaa   1647
Ile Val Gln Pro Val Glu Glu Ser Asp Asn Val Thr Gln Asp Met Lys
                435                 440                 445

gaa act gga cca gtt acg agc aga gaa tat gag gag aac ggg caa ata   1695
Glu Thr Gly Pro Val Thr Ser Arg Glu Tyr Glu Glu Asn Gly Gln Ile
            450                 455                 460

caa cat ggt aaa tca agt gat ccc aaa ttc tat tct tcg gtg tac cca   1743
Gln His Gly Lys Ser Ser Asp Pro Lys Phe Tyr Ser Ser Val Tyr Pro
        465                 470                 475

gag tat tgg gtt cct gtg cag cta tca gat gta cag ctg gag caa tac   1791
Glu Tyr Trp Val Pro Val Gln Leu Ser Asp Val Gln Leu Glu Gln Tyr
    480                 485                 490

tgt cag act ctc ttc tcc aaa tcc tta tct ctt tct tca ctt tcg aag   1839
Cys Gln Thr Leu Phe Ser Lys Ser Leu Ser Leu Ser Ser Leu Ser Lys
495                 500                 505                 510

att gat ctt gga gct cta gaa gaa act ctc aat tct gta aga aaa acc   1887
Ile Asp Leu Gly Ala Leu Glu Glu Thr Leu Asn Ser Val Arg Lys Thr
                515                 520                 525

tgt gac cat cca tac gtt atg gat gca tct ttg aaa caa ctg ctc acc   1935
Cys Asp His Pro Tyr Val Met Asp Ala Ser Leu Lys Gln Leu Leu Thr
            530                 535                 540

aag aat ctg gag ttg cat gaa atc ctg gat gta gaa att aaa gcg agc   1983
Lys Asn Leu Glu Leu His Glu Ile Leu Asp Val Glu Ile Lys Ala Ser
        545                 550                 555

ggg aaa ctt cac ctc ctt gat aaa atg ctt act cat ata aaa aag aat   2031
Gly Lys Leu His Leu Leu Asp Lys Met Leu Thr His Ile Lys Lys Asn
    560                 565                 570

ggt tta aaa gca gtt gtc ttc tac cag gca aca caa acc cct gaa ggg   2079
Gly Leu Lys Ala Val Val Phe Tyr Gln Ala Thr Gln Thr Pro Glu Gly
575                 580                 585                 590

ctt ctg ctt ggt aat att ctc gaa gat ttt gtg ggt caa aga ttt ggt   2127
Leu Leu Leu Gly Asn Ile Leu Glu Asp Phe Val Gly Gln Arg Phe Gly
                595                 600                 605

cca aaa tct tat gag cat ggg ata tat tcc tca aag aag aac tcc gct   2175
Pro Lys Ser Tyr Glu His Gly Ile Tyr Ser Ser Lys Lys Asn Ser Ala
            610                 615                 620

ata aac aat ttc aac aag gag agt caa tgc tgt gtt ctg ctg ttg gaa   2223
Ile Asn Asn Phe Asn Lys Glu Ser Gln Cys Cys Val Leu Leu Leu Glu
        625                 630                 635

aca cgt gcc tgc agt caa acc att aaa ctc ttg cga gct gat gcg ttt   2271
Thr Arg Ala Cys Ser Gln Thr Ile Lys Leu Leu Arg Ala Asp Ala Phe
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    640                 645                 650

att ctt ttt gga agc agc ttg aat cca tcg cat gat gtt aag cac gta   2319
Ile Leu Phe Gly Ser Ser Leu Asn Pro Ser His Asp Val Lys His Val
655                 660                 665                 670

gag aag ata aaa atc gag tca tgt tct gaa aga act aag ata ttc cga   2367
Glu Lys Ile Lys Ile Glu Ser Cys Ser Glu Arg Thr Lys Ile Phe Arg
                675                 680                 685

ttg tac tca gta tgt aca gtt gaa gaa aaa gcc ctg att ctg gct agg   2415
Leu Tyr Ser Val Cys Thr Val Glu Glu Lys Ala Leu Ile Leu Ala Arg
            690                 695                 700

caa aat atg cgg caa aat aaa gct gta gag aac cta aac cgc tct ctc   2463
Gln Asn Met Arg Gln Asn Lys Ala Val Glu Asn Leu Asn Arg Ser Leu
        705                 710                 715

acg cac gca ctg ctc atg tgg ggg gcg tca tac tta ttt gat aaa ctg   2511
Thr His Ala Leu Leu Met Trp Gly Ala Ser Tyr Leu Phe Asp Lys Leu
    720                 725                 730

gat cat ttt cac agc agt gaa act cca gat tca gga gtt tca ttt gaa   2559
Asp His Phe His Ser Ser Glu Thr Pro Asp Ser Gly Val Ser Phe Glu
735                 740                 745                 750

caa tct att atg gac ggc gtg att cat gaa ttc tcg tcc ata ctt tct   2607
Gln Ser Ile Met Asp Gly Val Ile His Glu Phe Ser Ser Ile Leu Ser
                755                 760                 765

tcc aaa ggt gga gaa gaa aat gaa gtc aag ctg tgt cta ctt ttg gag   2655
Ser Lys Gly Gly Glu Glu Asn Glu Val Lys Leu Cys Leu Leu Leu Glu
            770                 775                 780

gcc aag cat gct cag gga act tac agc agt gat tct act cta ttt ggt   2703
Ala Lys His Ala Gln Gly Thr Tyr Ser Ser Asp Ser Thr Leu Phe Gly
        785                 790                 795

gaa gac cat att aag ttg tca gat gaa gag agt cca aat ata ttt tgg   2751
Glu Asp His Ile Lys Leu Ser Asp Glu Glu Ser Pro Asn Ile Phe Trp
    800                 805                 810

tca aag ctg ttg ggg gga aaa aat cct atg tgg aaa tac cct tca gat   2799
Ser Lys Leu Leu Gly Gly Lys Asn Pro Met Trp Lys Tyr Pro Ser Asp
815                 820                 825                 830

act ccc caa agg aat cga aaa cga gtt cag tat ttt gag ggt tct gaa   2847
Thr Pro Gln Arg Asn Arg Lys Arg Val Gln Tyr Phe Glu Gly Ser Glu
                835                 840                 845

gcg agt ccc aaa act ggc gat ggt gga aat gca aag aag cga aag aag   2895
Ala Ser Pro Lys Thr Gly Asp Gly Gly Asn Ala Lys Lys Arg Lys Lys
            850                 855                 860

gct tct gat gat gtc act gat ccc cgg gtc act gat ccg cca gta gat   2943
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Ala Ser Asp Asp Val Thr Asp Pro Arg Val Thr Asp Pro Pro Val Asp
        865                 870                 875

gat gat gaa aga aag gcc tct ggg aag gat cac atg ggg gct ttg gag   2991
Asp Asp Glu Arg Lys Ala Ser Gly Lys Asp His Met Gly Ala Leu Glu
    880                 885                 890

tca cca aaa gtc ata aca ctc cag tca tca tgt aaa tct tct ggt aca   3039
Ser Pro Lys Val Ile Thr Leu Gln Ser Ser Cys Lys Ser Ser Gly Thr
895                 900                 905                 910

gat ggt aca ttg gat gga aat gat gct ttt ggc ttg tat tct atg ggc   3087
Asp Gly Thr Leu Asp Gly Asn Asp Ala Phe Gly Leu Tyr Ser Met Gly
                915                 920                 925

agc cat atc tct gga atc cca gag gat atg tta gct agt caa gat tgg   3135
Ser His Ile Ser Gly Ile Pro Glu Asp Met Leu Ala Ser Gln Asp Trp
            930                 935                 940

ggg aaa ata ccg gat gaa tca cag agg agg ctc cac act gtt tta aag   3183
Gly Lys Ile Pro Asp Glu Ser Gln Arg Arg Leu His Thr Val Leu Lys
        945                 950                 955

ccg aag atg gca aaa ctt tgc caa gtt ttg cat ctt tca gat gct tgc   3231
Pro Lys Met Ala Lys Leu Cys Gln Val Leu His Leu Ser Asp Ala Cys
    960                 965                 970

aca agc atg gtc gga aat ttt ctc gaa tat gtt att gaa aat cac cga   3279
Thr Ser Met Val Gly Asn Phe Leu Glu Tyr Val Ile Glu Asn His Arg
975                 980                 985                 990

atc tac gaa gag cca gcc act act ttt cag gca ttc cag ata gcc ctg   3327
Ile Tyr Glu Glu Pro Ala Thr Thr Phe Gln Ala Phe Gln Ile Ala Leu
                995                1000                1005

agt tgg att gca gcc ttg ttg gta aag caa att ctt agc cac aaa gaa   3375
Ser Trp Ile Ala Ala Leu Leu Val Lys Gln Ile Leu Ser His Lys Glu
           1010                1015                1020

tct ctg gtc cgt gca aat tct gaa tta gct ttc aaa tgc tct aga gta   3423
Ser Leu Val Arg Ala Asn Ser Glu Leu Ala Phe Lys Cys Ser Arg Val
       1025                1030                1035

gag gtg gat tat att tat tcg ata ttg tcc tgc atg aag agt ctg ttc   3471
Glu Val Asp Tyr Ile Tyr Ser Ile Leu Ser Cys Met Lys Ser Leu Phe
   1040                1045                1050

ctg gag cat aca caa ggt ttg cag ttc gat tgc ttt ggt act aat tct   3519
Leu Glu His Thr Gln Gly Leu Gln Phe Asp Cys Phe Gly Thr Asn Ser
1055                1060                1065                1070

aaa cag tca gtg gtt agc aca aaa cta gta aat gaa agt ctc tca ggg   3567
Lys Gln Ser Val Val Ser Thr Lys Leu Val Asn Glu Ser Leu Ser Gly
               1075                1080                1085
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gct aca gtg cgt gac gaa aag att aat acg aag tcg atg cga aat agc   3615
Ala Thr Val Arg Asp Glu Lys Ile Asn Thr Lys Ser Met Arg Asn Ser
          1090                1095                1100

tca gag gat gaa gag tgc atg act gag aag aga tgt agc cat tat agc   3663
Ser Glu Asp Glu Glu Cys Met Thr Glu Lys Arg Cys Ser His Tyr Ser
      1105                1110                1115

aca gca aca aga gat atc gaa aag act att agt ggc ata aaa aag aaa   3711
Thr Ala Thr Arg Asp Ile Glu Lys Thr Ile Ser Gly Ile Lys Lys Lys
  1120                1125                1130

tac aag aag caa gtg caa aag ctt gta caa gag cat gag gaa aag aaa   3759
Tyr Lys Lys Gln Val Gln Lys Leu Val Gln Glu His Glu Glu Lys Lys
1135                1140                1145                1150

atg gag ctg tta aat atg tat gca gac aag aag cag aaa ctt gaa act   3807
Met Glu Leu Leu Asn Met Tyr Ala Asp Lys Lys Gln Lys Leu Glu Thr
              1155                1160                1165

agt aaa agt gtg gaa gca gca gta att cgt att acc tgt tca cgg acc   3855
Ser Lys Ser Val Glu Ala Ala Val Ile Arg Ile Thr Cys Ser Arg Thr
          1170                1175                1180

agt act caa gtg ggt gat ctc aaa ctg ctg gat cat aat tat gaa aga   3903
Ser Thr Gln Val Gly Asp Leu Lys Leu Leu Asp His Asn Tyr Glu Arg
      1185                1190                1195

aag ttt gat gaa atc aaa agt gag aaa aat gaa tgc ctc aaa agt ctg   3951
Lys Phe Asp Glu Ile Lys Ser Glu Lys Asn Glu Cys Leu Lys Ser Leu
  1200                1205                1210

gag caa atg cac gag gtt gca aag aag aag ttg gct gag gat gaa gcc   3999
Glu Gln Met His Glu Val Ala Lys Lys Lys Leu Ala Glu Asp Glu Ala
1215                1220                1225                1230

tgt tgg att aat cgg ata aag agc tgg gca gct aaa tta aaa gtt tgt   4047
Cys Trp Ile Asn Arg Ile Lys Ser Trp Ala Ala Lys Leu Lys Val Cys
              1235                1240                1245

gtt ccc att caa agt ggc aat aac aag cat ttt agt ggt tca tca aac   4095
Val Pro Ile Gln Ser Gly Asn Asn Lys His Phe Ser Gly Ser Ser Asn
          1250                1255                1260

att tcc caa aat gct cct gat gta caa att tgc aat aat gct aac gtt   4143
Ile Ser Gln Asn Ala Pro Asp Val Gln Ile Cys Asn Asn Ala Asn Val
      1265                1270                1275

gaa gct act tac gct gat acg aat tgc atg gct tcc aag gtt aat caa   4191
Glu Ala Thr Tyr Ala Asp Thr Asn Cys Met Ala Ser Lys Val Asn Gln
  1280                1285                1290

gtg cca gaa gca gaa aac aca tta gga acc atg tcg ggt ggc agc act   4239
Val Pro Glu Ala Glu Asn Thr Leu Gly Thr Met Ser Gly Gly Ser Thr
1295                1300                1305                1310
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caa caa gtt cat gaa atg gtg gat gta aga aat gac gag aca atg gat   4287
Gln Gln Val His Glu Met Val Asp Val Arg Asn Asp Glu Thr Met Asp
               1315                1320                1325

gtc tca gct ttg tct cgt gaa cag ctt aca aag agc cag tcc aat gag   4335
Val Ser Ala Leu Ser Arg Glu Gln Leu Thr Lys Ser Gln Ser Asn Glu
           1330                1335                1340

cac gct tct atc act gtg cct gag att ttg att cct gct gac tgt caa   4383
His Ala Ser Ile Thr Val Pro Glu Ile Leu Ile Pro Ala Asp Cys Gln
       1345                1350                1355

gag gaa ttt gcg gcc ttg aac gtg cat ttg tca gaa gac cag aat tgt   4431
Glu Glu Phe Ala Ala Leu Asn Val His Leu Ser Glu Asp Gln Asn Cys
   1360                1365                1370

gac aga ata aca tct gcg gca tca gat gaa gat gtt tca tca agg gtg   4479
Asp Arg Ile Thr Ser Ala Ala Ser Asp Glu Asp Val Ser Ser Arg Val
1375                1380                1385                1390

cca gag gta tcc cag tca ctc gaa aat ctt tct gcc tcc ccc gag ttt   4527
Pro Glu Val Ser Gln Ser Leu Glu Asn Leu Ser Ala Ser Pro Glu Phe
               1395                1400                1405

tct cta aat aga gag gag gct ttg gtt aca aca gaa aat aga aga aca   4575
Ser Leu Asn Arg Glu Glu Ala Leu Val Thr Thr Glu Asn Arg Arg Thr
           1410                1415                1420

agt cat gtg ggt ttt gat act gat aac att ttg gac cag cag aat aga   4623
Ser His Val Gly Phe Asp Thr Asp Asn Ile Leu Asp Gln Gln Asn Arg
       1425                1430                1435

gaa gat tgt tct ctt gac caa gag att cct gac gag tta gcg atg cct   4671
Glu Asp Cys Ser Leu Asp Gln Glu Ile Pro Asp Glu Leu Ala Met Pro
   1440                1445                1450

gtg caa cat ctt gcg tct gtg gta gag act agg ggt gct gct gaa tct   4719
Val Gln His Leu Ala Ser Val Val Glu Thr Arg Gly Ala Ala Glu Ser
1455                1460                1465                1470

gat cag tat ggt caa gat ata tgt cct atg cct tct tca ctg gct gga   4767
Asp Gln Tyr Gly Gln Asp Ile Cys Pro Met Pro Ser Ser Leu Ala Gly
               1475                1480                1485

aag caa cct gac cca gca gca aac act gag agc gaa aat ctt gaa gaa   4815
Lys Gln Pro Asp Pro Ala Ala Asn Thr Glu Ser Glu Asn Leu Glu Glu
           1490                1495                1500

gca att gag cct cag tct gct ggt tca gaa aca gta gag act act gat   4863
Ala Ile Glu Pro Gln Ser Ala Gly Ser Glu Thr Val Glu Thr Thr Asp
       1505                1510                1515

ttt gct gca tca cat cag ggt gat caa gtt aca tgt cct ttg cta tct   4911
Phe Ala Ala Ser His Gln Gly Asp Gln Val Thr Cys Pro Leu Leu Ser
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1520                1525                1530

tca ccg act gga aat cag cct gcg cca gaa gca aat att gaa ggc caa   4959
Ser Pro Thr Gly Asn Gln Pro Ala Pro Glu Ala Asn Ile Glu Gly Gln
1535                1540                1545                1550

aat atc aac aca tca gct gag ccc cat gta gcg ggt cca gat gca gta   5007
Asn Ile Asn Thr Ser Ala Glu Pro His Val Ala Gly Pro Asp Ala Val
                1555                1560                1565

gag agt ggt gat tat gca gta ata gat cag gaa aca atg ggt gct cag   5055
Glu Ser Gly Asp Tyr Ala Val Ile Asp Gln Glu Thr Met Gly Ala Gln
            1570                1575                1580

gat gca tgc tct ctg cca tct gga tcg gtt gga act cag tct gac cta   5103
Asp Ala Cys Ser Leu Pro Ser Gly Ser Val Gly Thr Gln Ser Asp Leu
        1585                1590                1595

gga gca aac att gag ggt caa aat gtc aca aca gtg gct caa ctt ccc   5151
Gly Ala Asn Ile Glu Gly Gln Asn Val Thr Thr Val Ala Gln Leu Pro
    1600                1605                1610

aca gat gga tca gat gca gtt gta acc ggt gga tct cct gta tca gat   5199
Thr Asp Gly Ser Asp Ala Val Val Thr Gly Gly Ser Pro Val Ser Asp
1615                1620                1625                1630

cag tgt gcc cag gat gca tct cct atg cca tta tct tcg cct gga aat   5247
Gln Cys Ala Gln Asp Ala Ser Pro Met Pro Leu Ser Ser Pro Gly Asn
                1635                1640                1645

cac cct gat aca gca gtt aat atc gag ggt tta gat aac aca tca gta   5295
His Pro Asp Thr Ala Val Asn Ile Glu Gly Leu Asp Asn Thr Ser Val
            1650                1655                1660

gct gag cct cat ata agt gga tca gat gca tgt gaa atg gaa att tca   5343
Ala Glu Pro His Ile Ser Gly Ser Asp Ala Cys Glu Met Glu Ile Ser
        1665                1670                1675

gaa cct ggt ccc caa gta gag cgg tca acc ttt gca aat ctt ttc cat   5391
Glu Pro Gly Pro Gln Val Glu Arg Ser Thr Phe Ala Asn Leu Phe His
    1680                1685                1690

gaa ggt ggc gtg gag cat tca gca ggt gta aca gct ctt gtt cca tca   5439
Glu Gly Gly Val Glu His Ser Ala Gly Val Thr Ala Leu Val Pro Ser
1695                1700                1705                1710

ctt ctt aac aat ggt acg gaa cag att gcc gtt caa cct gtt cct caa   5487
Leu Leu Asn Asn Gly Thr Glu Gln Ile Ala Val Gln Pro Val Pro Gln
                1715                1720                1725

ata cct ttc cct gtg ttc aac gac ccg ttt ctg cat gaa ctg gag aag   5535
Ile Pro Phe Pro Val Phe Asn Asp Pro Phe Leu His Glu Leu Glu Lys
            1730                1735                1740

ttg cgg aga gaa tca gag aac tca aag aag act ttt gaa gaa aaa aaa   5583
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Leu Arg Arg Glu Ser Glu Asn Ser Lys Lys Thr Phe Glu Glu Lys Lys
      1745                1750                1755

tca atc ttg aaa gct gaa ctc gag agg aag atg gct gaa gta caa gca   5631
Ser Ile Leu Lys Ala Glu Leu Glu Arg Lys Met Ala Glu Val Gln Ala
   1760                1765                1770

gag ttt cga aga aaa ttt cat gag gta gaa gcc gag cat aac acc aga   5679
Glu Phe Arg Arg Lys Phe His Glu Val Glu Ala Glu His Asn Thr Arg
1775                1780                1785                1790

acg aca aag ata gag aag gat aag aat ctt gtt ata atg aac aaa ctg   5727
Thr Thr Lys Ile Glu Lys Asp Lys Asn Leu Val Ile Met Asn Lys Leu
               1795                1800                1805

ttg gcg aat gcg ttc ttg tcc aaa tgt act gac aag aag gta tct ccc   5775
Leu Ala Asn Ala Phe Leu Ser Lys Cys Thr Asp Lys Lys Val Ser Pro
          1810                1815                1820

tca gga gct cca agg ggt aaa att cag cag cta gca cag aga gca gca   5823
Ser Gly Ala Pro Arg Gly Lys Ile Gln Gln Leu Ala Gln Arg Ala Ala
      1825                1830                1835

caa gtg agt gca ctg aga aat tac att gct cct cag cag ctt cag gca   5871
Gln Val Ser Ala Leu Arg Asn Tyr Ile Ala Pro Gln Gln Leu Gln Ala
   1840                1845                1850

tct tct ttt cct gct cct gct ctg gtt tcg gct cct ctg caa ctt cag   5919
Ser Ser Phe Pro Ala Pro Ala Leu Val Ser Ala Pro Leu Gln Leu Gln
1855                1860                1865                1870

caa tca tca ttt cct gct cct ggt ccg gct cct ctg cag cct cag gca   5967
Gln Ser Ser Phe Pro Ala Pro Gly Pro Ala Pro Leu Gln Pro Gln Ala
               1875                1880                1885

tct tcg ttt cct tct tca gtc tct cgt cca tca gcc ctt ctt ctg aat   6015
Ser Ser Phe Pro Ser Ser Val Ser Arg Pro Ser Ala Leu Leu Leu Asn
          1890                1895                1900

ttt gcg gtc tgt cca atg cct cag ccc aga cag cct ctc ata tcc aac   6063
Phe Ala Val Cys Pro Met Pro Gln Pro Arg Gln Pro Leu Ile Ser Asn
      1905                1910                1915

ata gct cca act cca tca gtt act cct gca aca aat cca ggt ctg cgt   6111
Ile Ala Pro Thr Pro Ser Val Thr Pro Ala Thr Asn Pro Gly Leu Arg
   1920                1925                1930

tct cct gca cca cac cta aac tca tat aga cca tcc tct tca act ccc   6159
Ser Pro Ala Pro His Leu Asn Ser Tyr Arg Pro Ser Ser Ser Thr Pro
1935                1940                1945                1950

gtc gcc aca gct act cca acc tcg tca gtg cct cct caa gct ttg aca   6207
Val Ala Thr Ala Thr Pro Thr Ser Ser Val Pro Pro Gln Ala Leu Thr
               1955                1960                1965
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tat tca gct gtg tca att cag cag cag caa gaa caa caa ccg caa cag 6255
Tyr Ser Ala Val Ser Ile Gln Gln Gln Gln Glu Gln Gln Pro Gln Gln
1970 1975 1980

agc ttg agc agt gga ttg cag agc aac aat gaa gtg gtt tgt ctt tct 6303
Ser Leu Ser Ser Gly Leu Gln Ser Asn Asn Glu Val Val Cys Leu Ser
1985 1990 1995

gac gac gag tgacctaaga ggagagatgg ttagggtctt agttattgat 6352
Asp Asp Glu
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35 40 45

Pro Ala Ser Ala Thr Arg Lys Ser Glu Arg Leu Ala Pro Ser Pro Ala
50 55 60

Ser Val Ser Lys Lys Ser Gly Gly Ile Val Lys Asn Ser Thr Pro Ser
65 70 75 80

Ser Leu Arg Arg Ser Asn Arg Gly Lys Thr Glu Val Ser Leu Gln Ser
85 90 95

Ser Lys Gly Ser Asp Asn Ser Ile Arg Lys Gly Asp Thr Ser Pro Asp
100 105 110

Ile Glu Gln Arg Lys Asp Ser Val Glu Glu Ser Thr Asp Lys Ile Lys
115 120 125

Pro Ile Met Ser Ala Arg Ser Tyr Arg Ala Leu Phe Arg Gly Lys Leu
130 135 140

Lys Glu Ser Glu Ala Leu Val Asp Ala Ser Pro Asn Glu Glu Glu Leu

145 150 155 160

Val Val Val Gly Cys Ser Arg Arg Ile Pro Ala Gly Asn Asp Asp Val
165 170 175

Gln Gly Lys Thr Asp Cys Pro Pro Pro Ala Asp Ala Gly Ser Lys Arg
180 185 190

Leu Pro Val Asp Glu Thr Ser Leu Asp Lys Gly Thr Asp Phe Pro Leu
195 200 205

Lys Ser Val Thr Glu Thr Glu Lys Ile Val Leu Asp Ala Ser Pro Ile
210 215 220

Val Glu Thr Gly Asp Asp Ser Val Ile Gly Ser Pro Ser Glu Asn Leu
225 230 235 240

Glu Thr Gln Lys Leu Gln Asp Gly Lys Thr Asp Cys Ser Pro Pro Ala
245 250 255

Asn Ala Glu Ser Lys Thr Leu Pro Val Gly Glu Thr Ser Leu Glu Lys
260 265 270

Glu Tyr Pro Gln Lys Phe Gln Asp Asp Asn Thr Asp Cys Leu Pro Pro
275 280 285

Ala Asn Ala Glu Ser Lys Arg Leu Pro Val Gly Glu Thr Ser Leu Glu
290 295 300

Lys Asp Thr Asp Phe Pro Leu Lys Ser Thr Thr Glu Thr Gly Lys Met
305 310 315 320

Val Leu Tyr Ala Ser Pro Ile Val Glu Thr Arg Asp Asp Ser Val Ile
325 330 335

Cys Ser Pro Ser Thr Asn Leu Glu Thr Gln Lys Leu Leu Val Ser Lys
340 345 350

Thr Gly Leu Glu Thr Asp Ile Val Leu Pro Leu Lys Arg Lys Arg Asp
355 360 365

Thr Ala Glu Ile Glu Leu Asp Ala Cys Ala Thr Val Ala Asn Gly Asp
370 375 380

Asp His Val Met Ser Ser Asp Gly Val Ile Pro Ser Pro Ser Gly Cys
385 390 395 400

Lys Asn Asp Asn Arg Pro Glu Met Cys Asn Thr Cys Lys Lys Arg Gln
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Lys Val Asn Gly Asp Cys Gln Asn Arg Ser Val Cys Ser Cys Ile Val
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Gln Pro Val Glu Glu Ser Asp Asn Val Thr Gln Asp Met Lys Glu Thr
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Gly Pro Val Thr Ser Arg Glu Tyr Glu Glu Asn Gly Gln Ile Gln His
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Gly Lys Ser Ser Asp Pro Lys Phe Tyr Ser Ser Val Tyr Pro Glu Tyr
465                 470                 475                 480

Trp Val Pro Val Gln Leu Ser Asp Val Gln Leu Glu Gln Tyr Cys Gln
                485                 490                 495

Thr Leu Phe Ser Lys Ser Leu Ser Leu Ser Ser Leu Ser Lys Ile Asp
            500                 505                 510

Leu Gly Ala Leu Glu Glu Thr Leu Asn Ser Val Arg Lys Thr Cys Asp
        515                 520                 525

His Pro Tyr Val Met Asp Ala Ser Leu Lys Gln Leu Leu Thr Lys Asn
    530                 535                 540

Leu Glu Leu His Glu Ile Leu Asp Val Glu Ile Lys Ala Ser Gly Lys
545                 550                 555                 560

Leu His Leu Leu Asp Lys Met Leu Thr His Ile Lys Lys Asn Gly Leu
                565                 570                 575

Lys Ala Val Val Phe Tyr Gln Ala Thr Gln Thr Pro Glu Gly Leu Leu
            580                 585                 590

Leu Gly Asn Ile Leu Glu Asp Phe Val Gly Gln Arg Phe Gly Pro Lys
        595                 600                 605

Ser Tyr Glu His Gly Ile Tyr Ser Ser Lys Lys Asn Ser Ala Ile Asn
    610                 615                 620

Asn Phe Asn Lys Glu Ser Gln Cys Cys Val Leu Leu Leu Glu Thr Arg
625                 630                 635                 640

Ala Cys Ser Gln Thr Ile Lys Leu Leu Arg Ala Asp Ala Phe Ile Leu
                645                 650                 655

Phe Gly Ser Ser Leu Asn Pro Ser His Asp Val Lys His Val Glu Lys
            660                 665                 670

Ile Lys Ile Glu Ser Cys Ser Glu Arg Thr Lys Ile Phe Arg Leu Tyr
        675                 680                 685

Ser Val Cys Thr Val Glu Glu Lys Ala Leu Ile Leu Ala Arg Gln Asn
    690                 695                 700

Met Arg Gln Asn Lys Ala Val Glu Asn Leu Asn Arg Ser Leu Thr His
705                 710                 715                 720

Ala Leu Leu Met Trp Gly Ala Ser Tyr Leu Phe Asp Lys Leu Asp His
                725                 730                 735
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Phe His Ser Ser Glu Thr Pro Asp Ser Gly Val Ser Phe Glu Gln Ser
740 745 750

Ile Met Asp Gly Val Ile His Glu Phe Ser Ser Ile Leu Ser Ser Lys
755 760 765

Gly Gly Glu Glu Asn Glu Val Lys Leu Cys Leu Leu Leu Glu Ala Lys
770 775 780

His Ala Gln Gly Thr Tyr Ser Ser Asp Ser Thr Leu Phe Gly Glu Asp
785 790 795 800

His Ile Lys Leu Ser Asp Glu Glu Ser Pro Asn Ile Phe Trp Ser Lys
805 810 815

Leu Leu Gly Gly Lys Asn Pro Met Trp Lys Tyr Pro Ser Asp Thr Pro
820 825 830

Gln Arg Asn Arg Lys Arg Val Gln Tyr Phe Glu Gly Ser Glu Ala Ser
835 840 845

Pro Lys Thr Gly Asp Gly Gly Asn Ala Lys Lys Arg Lys Lys Ala Ser
850 855 860

Asp Asp Val Thr Asp Pro Arg Val Thr Asp Pro Pro Val Asp Asp Asp
865 870 875 880

Glu Arg Lys Ala Ser Gly Lys Asp His Met Gly Ala Leu Glu Ser Pro
885 890 895

Lys Val Ile Thr Leu Gln Ser Ser Cys Lys Ser Ser Gly Thr Asp Gly
900 905 910

Thr Leu Asp Gly Asn Asp Ala Phe Gly Leu Tyr Ser Met Gly Ser His
915 920 925

Ile Ser Gly Ile Pro Glu Asp Met Leu Ala Ser Gln Asp Trp Gly Lys
930 935 940

Ile Pro Asp Glu Ser Gln Arg Arg Leu His Thr Val Leu Lys Pro Lys
945 950 955 960

Met Ala Lys Leu Cys Gln Val Leu His Leu Ser Asp Ala Cys Thr Ser
965 970 975

Met Val Gly Asn Phe Leu Glu Tyr Val Ile Glu Asn His Arg Ile Tyr
980 985 990

Glu Glu Pro Ala Thr Thr Phe Gln Ala Phe Gln Ile Ala Leu Ser Trp
995 1000 1005

Ile Ala Ala Leu Leu Val Lys Gln Ile Leu Ser His Lys Glu Ser Leu
1010 1015 1020

Val Arg Ala Asn Ser Glu Leu Ala Phe Lys Cys Ser Arg Val Glu Val

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Asp Tyr Ile Tyr Ser Ile Leu Ser Cys Met Lys Ser Leu Phe Leu Glu
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His Thr Gln Gly Leu Gln Phe Asp Cys Phe Gly Thr Asn Ser Lys Gln
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Ser Val Val Ser Thr Lys Leu Val Asn Glu Ser Leu Ser Gly Ala Thr
1075 1080 1085

Val Arg Asp Glu Lys Ile Asn Thr Lys Ser Met Arg Asn Ser Ser Glu
1090 1095 1100

Asp Glu Glu Cys Met Thr Glu Lys Arg Cys Ser His Tyr Ser Thr Ala
105 1110 1115 1120

Thr Arg Asp Ile Glu Lys Thr Ile Ser Gly Ile Lys Lys Lys Tyr Lys
1125 1130 1135

Lys Gln Val Gln Lys Leu Val Gln Glu His Glu Glu Lys Lys Met Glu
1140 1145 1150

Leu Leu Asn Met Tyr Ala Asp Lys Lys Gln Lys Leu Glu Thr Ser Lys
1155 1160 1165

Ser Val Glu Ala Ala Val Ile Arg Ile Thr Cys Ser Arg Thr Ser Thr
1170 1175 1180

Gln Val Gly Asp Leu Lys Leu Leu Asp His Asn Tyr Glu Arg Lys Phe
185 1190 1195 1200

Asp Glu Ile Lys Ser Glu Lys Asn Glu Cys Leu Lys Ser Leu Glu Gln
1205 1210 1215

Met His Glu Val Ala Lys Lys Lys Leu Ala Glu Asp Glu Ala Cys Trp
1220 1225 1230

Ile Asn Arg Ile Lys Ser Trp Ala Ala Lys Leu Lys Val Cys Val Pro
1235 1240 1245

Ile Gln Ser Gly Asn Asn Lys His Phe Ser Gly Ser Ser Asn Ile Ser
1250 1255 1260

Gln Asn Ala Pro Asp Val Gln Ile Cys Asn Asn Ala Asn Val Glu Ala
265 1270 1275 1280

Thr Tyr Ala Asp Thr Asn Cys Met Ala Ser Lys Val Asn Gln Val Pro
1285 1290 1295

Glu Ala Glu Asn Thr Leu Gly Thr Met Ser Gly Gly Ser Thr Gln Gln
1300 1305 1310

Val His Glu Met Val Asp Val Arg Asn Asp Glu Thr Met Asp Val Ser
1315 1320 1325

Ala Leu Ser Arg Glu Gln Leu Thr Lys Ser Gln Ser Asn Glu His Ala
1330 1335 1340

Ser Ile Thr Val Pro Glu Ile Leu Ile Pro Ala Asp Cys Gln Glu Glu
345 1350 1355 1360

Phe Ala Ala Leu Asn Val His Leu Ser Glu Asp Gln Asn Cys Asp Arg
1365 1370 1375

Ile Thr Ser Ala Ala Ser Asp Glu Asp Val Ser Ser Arg Val Pro Glu
1380 1385 1390

Val Ser Gln Ser Leu Glu Asn Leu Ser Ala Ser Pro Glu Phe Ser Leu
1395 1400 1405

Asn Arg Glu Glu Ala Leu Val Thr Thr Glu Asn Arg Arg Thr Ser His
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Val Gly Phe Asp Thr Asp Asn Ile Leu Asp Gln Gln Asn Arg Glu Asp
425 1430 1435 1440

Cys Ser Leu Asp Gln Glu Ile Pro Asp Glu Leu Ala Met Pro Val Gln
1445 1450 1455

His Leu Ala Ser Val Val Glu Thr Arg Gly Ala Ala Glu Ser Asp Gln
1460 1465 1470

Tyr Gly Gln Asp Ile Cys Pro Met Pro Ser Ser Leu Ala Gly Lys Gln
1475 1480 1485

Pro Asp Pro Ala Ala Asn Thr Glu Ser Glu Asn Leu Glu Glu Ala Ile
1490 1495 1500

Glu Pro Gln Ser Ala Gly Ser Glu Thr Val Glu Thr Thr Asp Phe Ala
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Ala Ser His Gln Gly Asp Gln Val Thr Cys Pro Leu Leu Ser Ser Pro
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Thr Gly Asn Gln Pro Ala Pro Glu Ala Asn Ile Glu Gly Gln Asn Ile
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Asn Thr Ser Ala Glu Pro His Val Ala Gly Pro Asp Ala Val Glu Ser
1555 1560 1565

Gly Asp Tyr Ala Val Ile Asp Gln Glu Thr Met Gly Ala Gln Asp Ala
1570 1575 1580

Cys Ser Leu Pro Ser Gly Ser Val Gly Thr Gln Ser Asp Leu Gly Ala
585 1590 1595 1600

Asn Ile Glu Gly Gln Asn Val Thr Thr Val Ala Gln Leu Pro Thr Asp
1605 1610 1615

Gly Ser Asp Ala Val Val Thr Gly Gly Ser Pro Val Ser Asp Gln Cys
1620 1625 1630

Ala Gln Asp Ala Ser Pro Met Pro Leu Ser Ser Pro Gly Asn His Pro
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Asp Thr Ala Val Asn Ile Glu Gly Leu Asp Asn Thr Ser Val Ala Glu
1650 1655 1660

Pro His Ile Ser Gly Ser Asp Ala Cys Glu Met Glu Ile Ser Glu Pro
665 1670 1675 1680

Gly Pro Gln Val Glu Arg Ser Thr Phe Ala Asn Leu Phe His Glu Gly
1685 1690 1695

Gly Val Glu His Ser Ala Gly Val Thr Ala Leu Val Pro Ser Leu Leu
1700 1705 1710

Asn Asn Gly Thr Glu Gln Ile Ala Val Gln Pro Val Pro Gln Ile Pro
1715 1720 1725

Phe Pro Val Phe Asn Asp Pro Phe Leu His Glu Leu Glu Lys Leu Arg
1730 1735 1740

Arg Glu Ser Glu Asn Ser Lys Lys Thr Phe Glu Glu Lys Lys Ser Ile
745 1750 1755 1760

Leu Lys Ala Glu Leu Glu Arg Lys Met Ala Glu Val Gln Ala Glu Phe
1765 1770 1775

Arg Arg Lys Phe His Glu Val Glu Ala Glu His Asn Thr Arg Thr Thr
1780 1785 1790

Lys Ile Glu Lys Asp Lys Asn Leu Val Ile Met Asn Lys Leu Leu Ala
1795 1800 1805

Asn Ala Phe Leu Ser Lys Cys Thr Asp Lys Lys Val Ser Pro Ser Gly
1810 1815 1820

Ala Pro Arg Gly Lys Ile Gln Gln Leu Ala Gln Arg Ala Ala Gln Val
825 1830 1835 1840

Ser Ala Leu Arg Asn Tyr Ile Ala Pro Gln Gln Leu Gln Ala Ser Ser
1845 1850 1855

Phe Pro Ala Pro Ala Leu Val Ser Ala Pro Leu Gln Leu Gln Gln Ser
1860 1865 1870

Ser Phe Pro Ala Pro Gly Pro Ala Pro Leu Gln Pro Gln Ala Ser Ser
1875 1880 1885

Phe Pro Ser Ser Val Ser Arg Pro Ser Ala Leu Leu Leu Asn Phe Ala
1890 1895 1900

Val Cys Pro Met Pro Gln Pro Arg Gln Pro Leu Ile Ser Asn Ile Ala

905 1910 1915 1920

Pro Thr Pro Ser Val Thr Pro Ala Thr Asn Pro Gly Leu Arg Ser Pro
1925 1930 1935

Ala Pro His Leu Asn Ser Tyr Arg Pro Ser Ser Ser Thr Pro Val Ala
1940 1945 1950

Thr Ala Thr Pro Thr Ser Ser Val Pro Pro Gln Ala Leu Thr Tyr Ser
1955 1960 1965

Ala Val Ser Ile Gln Gln Gln Gln Glu Gln Gln Pro Gln Gln Ser Leu
1970 1975 1980

Ser Ser Gly Leu Gln Ser Asn Asn Glu Val Val Cys Leu Ser Asp Asp
985 1990 1995 2000

Glu

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